# Trajectories of urinary C–C motif chemokine ligand 14 (CCL14) and the persistence of severe acute kidney injury during critical illness

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## Introduction

In critically ill patients with established stage 2-3 acute kidney injury (AKI) elevated urinary C-C-motif chemokine ligand 14 (CCL14) has been shown to predict persistence of severe kidney injury [1,2], however the time-course of changes in CCL14 and its relationship to persistent severe AKI has not been described.

## Methods

Using existing data from two multicenter studies (Ruby and Sapphire) in mixed populations of critically ill adults, we analysed 3 consecutive measurements of urinary CCL14 taken at 12-hour intervals after development of moderate to severe AKI. CCL14 concentrations were measured using the NEPHROCLEAR™ CCL14 Test on the Astute 140® Meter (Astute Medical Inc., San Diego, CA). Primary endpoint was the development of persistent severe AKI, defined as 72 consecutive hours of stage 3 AKI or death or receipt of dialysis prior to 72h. We hypothesized that, trajectories of urinary CCL14 would provide additional information as to the likelihood of persistent severe AKI over single measurements. We stratified the CCL14 concentrations into three levels: Low (≤1.3 ng/mL), Medium (>1.3 to ≤13 ng/mL), and High (>13 ng/mL) based on previously determined clinical-risk cutoffs [3], and grouped patients by the pattern of CCL14 levels across the 3 samples.

## Table

| Variable | Odds Ratio | 95% CI | p-value |
|---|---|---|---|
| Initial Category: M | 9.91 | 4.64 – 23.3 | < 0.001 |
| Initial Category: H | 107 | 39.0 – 326 | < 0.001 |
| Change in Category: Decrease | 0.20 | 0.08 – 0.45 | < 0.001 |
| Change in Category: Increase | 4.04 | 1.75 – 9.46 | 0.001 |

*Multivariable logistic regression model for PS-AKI Endpoint with initial CCL14 category and change in CCL14 category over the first day as predictor variables. Reference levels: Initial Category: L and Change in Category: Stable.*

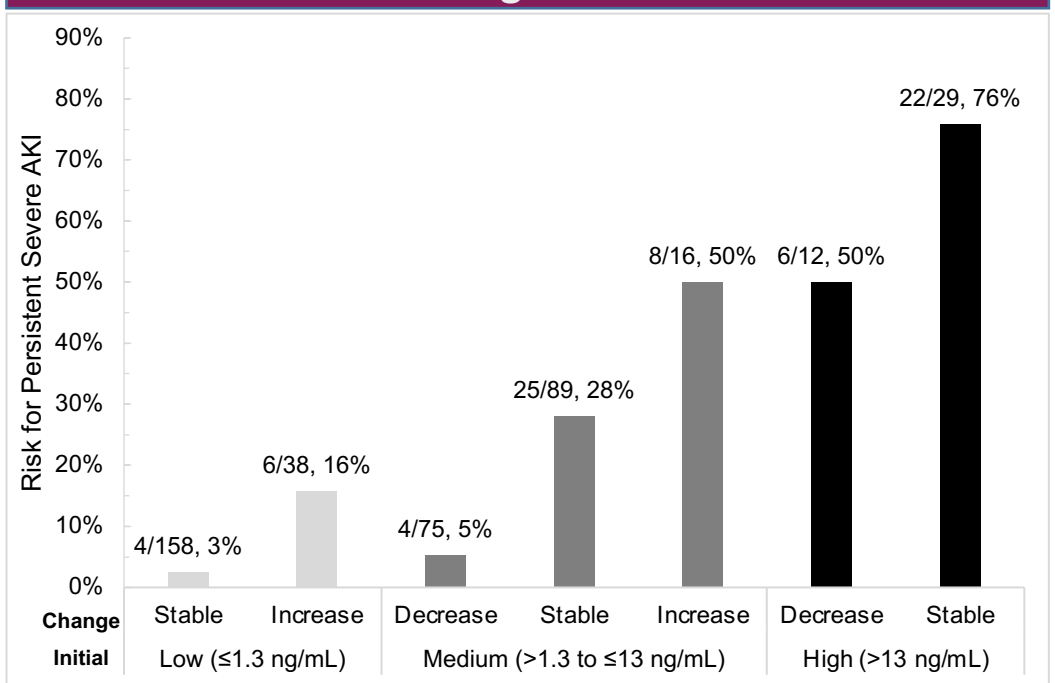
## References

1. Hoste, E, 2020. Intensive care medicine, 46:943-953.
2. Bagshaw, S.M, 2021. Critical Care, 25:1-8.
3. Koyner, J.L, 2021. Manuscript submitted for review.

## Results

417 patients (Median age 65, 59% male) had 3 consecutive CCL14 measurements and were included, of which 75 developed persistent severe AKI. Initial CCL4 levels were low in 196 (47%), medium in 180 (43%) and high in 41 (9.8%). As previous described [3] initial CCL14 category strongly correlated with primary endpoint, and in a majority of cases (66%) CCL14 category was unchanged from first to last timepoint (Figure). In multivariable logistic regression, accounting for initial CCL14 category, a decrease in CCL14 category in the first 24h was associated with decreased risk of persistent severe AKI, odds ratio (OR) 0.2 (95% CI 0.08 – 0.45, p < 0.001) and an increase in category with increased risk, OR 4.04 (1.75 – 9.46, p=0.001).

## Figure




## Discussion

In critical illness assessment of kidney function using creatinine may be impeded by falls in creatinine generation. Here kidney stress was detected in 86% of cases whereas creatinine defined AKI was only observed in 40%. When kidney function was assessed using a measure less-confounded by muscle mass change (Cystatin-c) severity of early kidney stress identified worse kidney function at ICU discharge. This was not observed using Creatinine. TIMP-2.IGFBP-7 may help risk-stratify long term renal function following critical illness. Future evaluation of kidney biomarker tests in critical illness should consider using Cystatin C rather than Creatinine to assess kidney outcomes.

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